Title
Failed ISCHEMIA Trial or Failed Ischemia Testing?

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Anatomic Burden OutPerforms Ischemic Burden

From “COURAGE” to “ISCHEMIA”

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Treatment of stable ischemic heart disease remains controversial due to lack of proper measures to identify the vulnerable patient who will suffer acute coronary events. Imaging modalities can identify rupture-prone coronary plaques but studies have found that most plaque ruptures without causing clinical events (1). High risk plaques identified by CT Angiogram (CTA) was found to be predictive of acute coronary events (ACS) in a large cohort study but the extent of atherosclerotic burden was a confounder (2). As such, numerous studies have suggested total atherosclerotic plaque burden as the main determinant of adverse patient outcomes (3,4). Coronary artery calcium (CAC) is a highly specific surrogate for coronary atherosclerosis burden and is the most predictive single cardiovascular risk marker in asymptomatic persons (5). The greater the atherosclerotic plaque burden, the more likely plaque ruptures will occur and the greater the probability that one of them triggers vascular thrombosis and a clinical event (6).

For many decades, inducible myocardial ischemia detected by myocardial perfusion stress testing has been used to guide therapy; however, it has been shown to be imperfect to predict significant stenosis in the coronary tree at time of angiography. Inducible ischemia happens due to supply-demand mismatch, and due to its chronicity, it allows myocardial preconditioning and cellular adaptations, which reduce the risk of acute myocardial infarction and ventricular arrhythmia. The idea that revascularization benefits patients with high ischemic burden stem from an observational study by Hachamovitch et al.(7) in 2003 which showed as the amount of inducible ischemia increases, there is more survival benefit in patients with revascularization compared to medical therapy. As COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) (8) trial failed to show benefits of revascularization over optimal medical therapy (OMT)in stable CAD patients. One possible explanation was that among 60% of patients enrolled in COURAGE trial after nuclear stress imaging, most had less than moderate ischemia (i.e. < 10% ischemic myocardium) and this factor was suggested to have contributed to the overall neutral results of the trial (9).

What would be the results of the COURAGE trial if most of the patients had moderate to severe ischemia instead of mild ischemia? A subgroup analysis from the COURAGE trial reported no reduction in death or MI among patients with moderate to severe ischemia compared with mild ischemia (10). Another substudy from the COURAGE trial looked at 314 patients with baseline and follow up nuclear stress test and showed that revascularization with OMT resulted in greater reduction in ischemic burden compared with

OMT alone (11). Similarly, a nuclear substudy of the BARI 2D (Randomized trial of Therapies for Type II Diabetes and CAD) trial suggested left ventricular ejection fraction (LVEF), but not the percent of ischemic myocardium, predicted event rates (12). A subgroup of STITCH (Surgical Treatment for Ischemic Heart Disease) trial further indicated that the presence of inducible ischemia on stress testing in patients with CAD and severe left ventricular dysfunction is not associated with worse prognosis and does not identify those with greater therapeutic benefit from surgical revascularization (13). Finally, Mancini et al.(14) showed in COURAGE trial that when both anatomic burden and ischemic burden of disease at baseline were considered concomitantly, anatomic burden was a consistent predictor of death, MI, and non-ST elevation MI, whereas ischemic burden was not. Also, the 5-year results of the SCOT-HEART (Scottish Computed Tomography of the Heart) study suggested that anatomic testing (CTA) lowers the rate of death or non-fatal MI by 41% greater than traditional stress testing (15).

The failure of the COURAGE and the BARI 2D trials suggested a need for another large randomized trial, but at this time, to enroll more high-risk patients to get better revascularization results with percutaneous coronary intervention (PCI). Once again, functional testing, but now with moderate to severe ischemia, was chosen as a measure to select high-risk patients. This algorithm was incorporated in the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) (16) trial where 5179 patients with at least moderate ischemia (i.e. >10% ischemic myocardium) were randomized to PCI plus OMT or OMT alone. The large sample size was thought to overcome any sample size limitations in the previous subgroup analysis. The ISCHEMIA trial failed to show any difference in outcomes from PCI plus OMT compared to OMT alone. However, when stratifying for outcomes by severity of ischemia and anatomy (17), a strong association was found between extent and severity of CAD and risk of death and MI. There was no association between ischemia severity and death. The 4-year all-cause mortality event rate in patients with 3-vessel disease, 2-vessel disease, and 1-vessel disease (all detected by CTA) were 7%, 5.3%, and 2% respectively ($p<0.001$). The mortality rate in the severely ischemic group, moderately ischemic group, and mildly ischemic group (detected by stress tests) were 5.8 %, 6.6%, and 9.1% respectively (worsening outcomes with more mild ischemia). The authors concluded that anatomy (by CTA) was more predictive of outcomes than ischemia, and there was a very strong association between extent and severity of atherosclerosis and risk of death and MI.

The sum of currently available literature suggests that the severity of ischemia based on stress testing does not identify high-risk patients. If it does so as in some observational studies, then it is because patients with high ischemic burden are likely to also have high anatomic burden which can indeed trigger vascular thrombosis. Perhaps an algorithm of CTA first, then lesion specific ischemia (such as selective use of FFR (Fractional Flow

Reserve) or FFR_{CT}) to target lesion-specific ischemia would fare better against OMT alone (18).

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